Blossoming contusions: identifying factors contributing to the expansion of traumatic intracerebral hemorrhage

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OBJECTIVE Traumatic brain injury (TBI) remains a significant cause of neurological morbidity and mortality. Each year, more than 1.7 million patients present to the emergency department with TBI. The goal of this study was to evaluate the prognosis of traumatic cerebral intraparenchymal hemorrhage (tIPH), to develop subclassifications of these injuries that relate to prognosis, and to provide a more comprehensive assessment of hemorrhagic progression contusion (HPC) by analyzing the rate at which tIPH “blossom” (i.e., expansion), depending on a variety of intrinsic and modifiable factors.

METHODS In this retrospective study, 726 patients (age range 0–100 years) were admitted to a level 1 trauma center with tIPH during an 8-year period (2005–2013). Of these patients, 491 underwent both admission and follow-up head CT (HCT) within 72 hours. The change in tIPH volume over time, the expansion rate, was recorded for all 491 patients. Effects of prehospital and in-hospital variables were examined using ordinal response logistic regression analyses. These variables were further examined using multivariate linear regression analysis to accurately predict the extent to which a hemorrhage will progress.

RESULTS Of the 491 (67.6%) patients who underwent both admission and follow-up HCT, 368 (74.9%) patients experienced HPC. These hemorrhages expanded on average by 61.6% (4.76 ml) with an average expansion rate of 0.71 ml per hour. On univariate analysis, certain patient characteristics were significantly ($p < 0.05$) related to HPC, including age (> 60 years), admission Glasgow Coma Scale score, blood alcohol level, international normalized ratio, absolute platelet count, transfusion of platelets, concomitant anticoagulation and antiplatelet medication, the initial tIPH volume on admission HCT, and ventriculostomy. Increased expansion rate was significantly associated with patient disposition to hospice or death ($p < 0.001$). To determine which factors most accurately predict overall patient disposition, an ordinal-response logistic regression identified systolic blood pressure, Injury Severity Score, admission Glasgow Coma Scale score, follow-up scan volume, transfusion of platelets, and ventriculostomy as predictors of patient discharge disposition following tIPH. A multivariate logistic regression identified several prehospital and in-hospital variables (age, Injury Severity Score, blood alcohol level, initial scan volume, concomitant epidural hematoma, presence of subarachnoid hemorrhage, transfusion of platelets, and ventriculostomy) that predicted the volumetric expansion of tIPH. Among these variables, the admission tIPH volume by HCT proved to be the factor most predictive of HPC.

CONCLUSIONS Several factors contribute to the rate at which traumatic cerebral contusions blossom in the acute posttraumatic period. Identifying the intrinsic and modifiable aspects of cerebral contusions can help predict the rate of expansion and highlight potential therapeutic interventions to improve TBI-associated morbidity and mortality.

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KEY WORDS intraparenchymal hemorrhage; traumatic brain injury; hemorrhagic progression of contusion; volumetric progression; intracerebral hemorrhage; trauma

ABBREVIATIONS AIC = Akaike information criterion; BAL = blood alcohol level; EDH = epidural hematoma; GCS = Glasgow Coma Scale; HCT = head CT; HPC = hemorrhagic progression of contusion; INR = international normalized ratio; ISS = Injury Severity Score; NISS = New Injury Severity Score; SAH = subarachnoid hemorrhage; SBP = systolic blood pressure; SDH = subdural hematoma; TBI = traumatic brain injury; tIPH = traumatic intraparenchymal hemorrhage.

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THROUGHOUT the world, traumatic brain injury (TBI) remains a significant cause of neurological morbidity and mortality.^{35,36} Annually in the United States, an estimated 1.7 million people experience TBI, resulting in 1.4 million emergency department visits, 270,000 hospitalizations, and 53,000 deaths. Moreover, nearly 5.3 million people live with disability due to TBI (<http://www.uab.edu/medicine/tbi/uab-tbi-information-network/bims-infosheets>).^{3,10,23,31} The most common mass lesions associated with TBI are hematomas and contusions, which occur in 13%–35% of patients following TBI.^{4,6,15,24,37} Traumatic contusions, or traumatic intraparenchymal hemorrhages (tIPH), are a type of TBI that can lead to lifelong cognitive, physical, and psychological disability.

Hemorrhagic progression of contusion (HPC) is a potential complication of tIPH and is defined as an increase in hemorrhage volume over time.^{1,6,7,25,32,39} HPC can be described as an initial 3D expansion followed by either reduction in volume or further expansion.^{6,22} HPC, which occurs in the first few hours after head trauma, has been demonstrated in 38%–63% of TBI patients. Studies investigating HPC have identified initial size of injury, coagulopathy, age, sex, and concurrent noncontusion TBI as the clinical variables correlated with HPC.^{1,32} In one of the largest tIPH cohorts, Cepeda and colleagues identified 782 patients and found a correlation between HPC and multiple contusions, smaller initial volume, acute subdural hematoma (SDH), cisternal compression, older patient age, hypoxia, falls, and decompressive craniectomy.⁶ However, large multivariable studies with volumetrically measured TBI are sparse, and no such study examining the various clinical influences on rates of volumetric hemorrhage expansion has previously been performed.³⁵

Currently, there is no standardized protocol for the identification of HPC and its risk factors, clinical course, prognosis, and management. The aim of this retrospective study is to provide a more comprehensive assessment of HPC by analyzing the rate at which tIPHs evolve as a function of relevant prehospital and in-hospital clinical factors. Additionally, we aim to describe correlations between clinical variables and HPC in a population of consecutive TBI patients presenting to a level 1 trauma center. Finally, we aim to use such variables to predict the extent to which a hemorrhage will progress and to describe the prognostic significance of HPC by investigating its relationship to patient outcome.

Methods

Patient Population and Demographics

After obtaining institutional review board approval, we conducted a retrospective observational study of all patients with tIPH who presented to the emergency department at Rhode Island Hospital, a level 1 trauma center in Providence, Rhode Island, during an 8-year period (January 2005 to December 2013). A standardized data collection spreadsheet was used, allowing trauma service clinicians to record multiple demographic and clinical variables for each patient (<https://www.lifespan.org/centers-services/trauma-center-rhode-island-hospital/trauma-patient-registry>). From the initial population of 726

consecutive tIPH patients presenting to our trauma center, we excluded all patients from our expansion analysis who did not undergo follow-up head CT (HCT) imaging within 72 hours after injury. After application of exclusion criteria, 491 tIPH patients remained, with admission and follow-up axial HCT scans obtained within 72 hours of injury.

Demographic and clinical data included the following: age, sex, admission systolic blood pressure (SBP), mechanism of injury (fall, motor vehicle collision, or assault and other), presenting Glasgow Coma Scale (GCS) score, Injury Severity Score (ISS), New Injury Severity Score (NISS), blood alcohol level (BAL), international normalized ratio (INR), absolute platelet count, contusion size at admission, time to first HCT, time between HCT sessions, additional intracranial hemorrhage (epidural hematoma [EDH], subarachnoid hemorrhage [SAH], or subdural hematoma [SDH]), medical interventions and procedures (use of anticoagulation/antiplatelet medication, platelet transfusion, craniotomy or craniectomy, or ventriculostomy), and discharge disposition (home, skilled nursing facility, or death/hospice). The distribution based on age and sex of our tIPH study population is shown in Fig. 1.

Imaging Analysis

The rate of HPC was calculated as the difference in volume between the first and second HCT scans divided by the time between the scans. Presence of tIPH was confirmed by both junior and attending radiologists, emergency physicians, and neurosurgeons. We used General Electric 3D imaging software to calculate the volumes of the cerebral contusions using each 5-mm HCT slice (Fig. 2). Furthermore, the presence of an additional intracerebral hemorrhage, SDH, EDH, or SAH was noted.

Statistical Analysis

Patient prehospital and in-hospital characteristics are given as percentages and means (SD). Distribution of the data was tested using quantile-quantile plots and the Shapiro-Wilk test for normal distribution. All variables were nonnormally distributed, and, therefore, nonparametric tests (Kolmogorov-Smirnov test and Kruskal-Wallis test) were used for analysis. Scatter plots were visually reviewed to find relationships between expansion rate and each clinical variable. Furthermore, multicollinearity testing with Pearson product-moment correlation coefficients was performed to eliminate confounding variables ($\rho > 0.7$).

First, Welch's t-test for equality of variance was used to compare the demographic and clinical differences between patients who underwent repeat HCT in the acute period ($n = 491$) and those who did not ($n = 235$). This was done to determine if patients who underwent repeat brain CT were distinct from patients who did not. For patients who underwent repeat brain CT, univariate comparisons were performed using Welch's 2-tailed t-test to identify demographic and clinical differences between tIPH patients with HPC ($n = 367$) and patients with no contusion expansion ($n = 124$). Levene's test of equality of variances was used to test the assumption of homogeneity of variance between samples for each variable ($F < 0.05$).

Next, we applied ordinal-response logistic regres-

FIG. 1. Histogram showing the age and sex distribution of the tIPH study population.

sion and multiple linear regression to establish predictive models of patient disposition and hemorrhage volume on repeat HCT, respectively. Ordinal-response logistic regression was performed using patient disposition as the dependent variable with categories death/hospice, skilled nursing facility, and home. Sex, age, SBP, ISS, NISS, GCS score, BAL, admission scan volume, follow-up scan volume, time between admission and follow-up scans, presence of EDH, presence of SDH, presence of SAH, platelet transfusion, ventriculostomy, and performance of a craniotomy or craniectomy were used as explanatory variables. Patients missing these data were removed from analysis. The Akaike information criterion (AIC) was used to select the best model. Goodness of fit was evaluated by

comparison of expected and actual counts as well as predictive power. Multiple linear regression was performed using the follow-up scan volume as the dependent variable and sex, age, SBP, ISS, NISS, GCS score, BAL, admission scan volume, presence of EDH, presence of SDH, presence of SAH, platelet transfusion, ventriculostomy, and performance of craniotomy or craniectomy as independent variables. Patients missing these data ($n = 69$) were removed from analysis. AIC was again used to select the best model. Goodness of fit was measured by correlation coefficient and residual plot. Model residuals were evaluated both graphically with quantile-quantile plots and by Kolmogorov-Smirnov test for normality.

Statistical analysis used an alpha level of 0.05 with a

FIG. 2. Volumetric analysis used to calculate volumes of cerebral contusions. **A:** Noncontrast HCT with tIPH. **B:** Three-dimensional volumetric model of tIPH. **C:** Volumetric model of hemorrhage superimposed on the 3D rendering of a patient's skull.

FIG. 3. Graph displaying the difference between HPC patients and the entire population in regard to time (hours) from brain injury to follow-up HCT.

95% confidence interval. All statistical analyses were performed using MATLAB version r2015a for Macintosh (Mathworks).

Results

Study Population

A total of 726 patients with tIPH were retrospectively reviewed in detail from our database of more than 8412 TBI patients admitted to our level 1 trauma center during an 8-year period. From this cohort, we found that 491 (67.6%) underwent both admission and follow-up HCT, allowing for assessment of HPC. Of these, 353 (72%) patients were male and 138 (28%) patients were female. The mean age was 50 years (SD 24), ranging from 0 to 100 years. Type of injury fell into 3 categories: blunt, penetrating, and other; more than 96% of injuries were blunt. Moreover, the mechanism of injury was separated into more evenly distributed categories: falls (66%), motor vehicle collisions (30%), and assaults and other (4%). The mean time from injury to admission HCT was 4 hours, while the mean time between first and follow-up HCT was 9 hours. Of the patients with a recorded time of injury, the difference between patients experiencing blossoming (i.e., HPC) and the entire population in regard to time (hours) from brain injury to follow-up HCT is shown in Fig. 3. Of the 491 patients in our analysis, the average admission SBP was 137 mm Hg, the GCS score was 11.8, the INR was 1.38, and the absolute platelet count was $130.5 \times 10^9/L$. Furthermore, 8.3% of patients received a platelet transfusion, 7.5% received a craniotomy or craniectomy, 6.9% received a ventriculostomy, 44.1% were discharged home, 46.3% were discharged to a skilled nursing facility,

and 9.6% of patients died. Aside from the 491 patients with follow-up HCT scans, the remaining 235 (32.4%) patients did not undergo repeat brain imaging following the initial HCT imaging session. The admission data for these 2 groups are compared in Table 1. Comparing the means of these 2 groups, t-tests showed a significant increase in the follow-up HCT population's age ($p = 0.019$), SBP ($p = 0.012$), BAL ($p = 0.003$), presence of EDH ($p < 0.001$), presence of SDH ($p = 0.005$), presence of SAH ($p < 0.001$), ventriculostomy ($p < 0.001$), craniotomy or craniectomy ($p = 0.008$), discharge to home ($p = 0.001$), and discharge to hospice/death ($p = 0.045$). Furthermore, t-tests between these 2 groups showed a significant increase regarding discharge to skilled nursing facility in the single HCT group.

Univariate Analysis: HPC Versus No HPC

Of the 491 patients with an admission and follow-up HCT, tIPH progression occurred in 367 (74.7%) patients, while no progression occurred in 124 (25.3%) patients. The admission data for these 2 groups are compared in Table 2. Between these groups, there were no significant differences in demographic and clinical data regarding sex, SBP, BAL, platelet transfusion, time to first HCT imaging session, time between HCT imaging sessions, presence of EDH and SAH, ventriculostomy, craniotomy or craniectomy, and discharge to skilled nursing facility. A nonsignificant commensurate trend was observed between BAL and HPC ($p = 0.0587$). There were significant differences regarding age ($p = 0.02$), ISS ($p = 0.004$), NISS ($p = 0.02$), GCS score ($p = 0.009$), absolute platelet count ($p = 0.023$), presence of SDH ($p = 0.05$), and patient disposition, including discharge to home ($p = 0.01$) and discharge

to hospice/death ($p < 0.001$). Looking closer at patient outcome, the group that was discharged home had a significantly lower proportion of patients who experienced HPC, while the group that was discharged to hospice or died had a significantly higher proportion of patients with HPC.

Univariate Analysis: Expansion Rate

We reviewed the 491 tIPH patients with both initial and follow-up HCTs from more than 8412 TBI patients admitted to our level 1 trauma center in an 8-year period. The mean expansion rate of tIPH among all patients with HPC was 0.71 ml/hr (SD 1.8). Continuous variables were categorized using clinically relevant cutoffs. There were significant differences in the expansion rate of tIPH based on age, GCS score, BAL, INR, absolute platelet count, platelet transfusion, use of anticoagulation or antiplatelet medication, initial size of hemorrhage on admission, time between HCT sessions, and ventriculostomy (Table 3). For patient disposition, progression data show a significant difference in expansion rate related to the patient's outcome in the acute setting. Overall, the expansion rate of a patient's hemorrhage was significantly increased in patients who were discharged to hospice or died compared with those who were discharged home in the acute setting.

Multivariate Analysis

We further evaluated the multivariable interaction of the demographic and clinical characteristics for their ability to predict the outcome and disposition of each patient. Our models address our main hypotheses that HPC is the result of potentially modifiable patient factors, and HPC can impact short-term patient outcomes.

The ordinal-response logistic regression with minimum AIC selected age, SBP, ISS, GCS score, follow-up scan volume, platelet transfusion, and ventriculostomy as predictors of patient disposition following tIPH. Variables from 422 patients were included in this analysis because patients with missing data ($n = 69$) were removed from consideration. Variable coefficients, odds ratios, and p values for each variable's contribution to likelihood of death/hospice are listed in Table 4. The odds ratios for death/hospice for real-valued variables, including age, SBP, ISS, GCS score, and second scan volume are also shown in Fig. 4. The OR of having medical decline to the point of death or discharge to hospice was 1.073 (95% CI 1.059–1.088) for each additional year of age; 0.964 (95% CI 0.921–1.009) for every 5-point increase in SBP; 1.091 (95% CI 1.059–1.125) and 0.871 (95% CI 0.820–0.926) for every point increase in ISS and GCS score, respectively; 1.031 (95% CI 1.013–1.049) for each milliliter increase in tIPH volume; 1.802 (95% CI 0.840–3.866) if the patient underwent a platelet transfusion; and 14.78 (95% CI 5.452–40.080) if the patient required ventriculostomy.

Next, we analyzed factors influencing the second scan volume of a patient's tIPH given the presenting demographic and clinical characteristics. The linear regression with minimum AIC selected the variables age, NISS, BAL, admission scan volume, presence of EDH, presence of SAH, platelet transfusion, and ventriculostomy as those that collectively predicted the volume on the second scan.

TABLE 1. Comparison of the tIPH population that underwent follow-up HCT versus the population that did not undergo repeat imaging

Admission Variable	Follow-Up HCT*		p Value
	Yes (n = 491)	No (n = 235)	
Age in yrs	50.3	45.2	0.019†
Male	72% (45%)	68% (60%)	0.302
SBP in mm Hg	137 (26.3)	132 (26.3)	0.012†
ISS	17.7 (9.9)	17.3 (10.2)	0.695
NISS	25.5 (13.2)	24.9 (14.7)	0.669
GCS score	11.8 (4.4)	12.1 (4.6)	0.289
BAL in mg/dl	61.5 (105.5)	38.3 (91.4)	0.003†
INR	1.379 (1.186)	1.206 (0.261)	0.144
Platelet transfusion	8.3% (28%)	5.3% (22%)	0.121
Time to 1st scan in hrs	3.9701 (3.4)	4.223 (3.9)	0.62452
Additional intracranial bleed			
EDH	24.8% (44%)	13.3% (35%)	1.273×10^{-4} †
SDH	43.4% (50%)	32.7% (47%)	0.005†
SAH	48.2% (50%)	32.3% (47%)	4.4×10^{-5} †
Craniectomy	7.5% (26%)	3.1% (17%)	0.008†
Use of ventriculostomy	6.9% (24%)	1.3% (10%)	5.479×10^{-5} †
Discharge disposition			
Home	44.1% (50%)	57.3 (50%)	0.001†
SNF	46.3% (50%)	27.6 (45%)	7.386×10^{-7} †
Hospice/death	9.59% (29%)	15.1 (36%)	0.045

SNF = skilled nursing facility.

* Values are presented as the mean (SD) unless stated otherwise.

† Significant following Benjamini-Hochberg procedure ($q = 0.05$, $m = 18$).

Patients with missing data ($n = 74$) were again removed from consideration. Variable main effects, multiplicative (i.e., interaction) effects, p values, and correlation coefficients (partial r^2) are shown in Table 5. Overall, the regression had a correlation coefficient of 0.529. Multiplicative effects for real-valued variables are shown in Table 5. A quantile-quantile plot of residuals is shown in Fig. 5. The Kolmogorov-Smirnov test for normality did not demonstrate that the model's residuals were nonnormally distributed ($p = 0.447$).

Discussion

Many factors contribute to the rate of contusion expansion after TBI. Understanding each individual variable's contribution to this volumetric progression could potentially lead to strategies to improve overall patient outcomes. Because complex interactions of each patient's intrinsic and modifiable presenting characteristics could obscure what combination of factors predict either an idle or rapidly expanding tIPH, we assessed prehospital and in-hospital variables and their relation to expansion rate

TABLE 2. Comparison of patients with tIPH who experienced HPC and those who did not

Admission Characteristics	HPC*		p Value
	Yes (n = 367)	No (n = 124)	
Age in yrs	51.7 (588.98)	45.9 (628.86)	0.023717
Male	0.7248 (0.20)	0.688 (0.21639)	0.44143
SBP in mm Hg	137.42 (685.59)	137.07 (716.1)	0.90026
ISS	18.281 (112.01)	15.808 (54.027)	0.0042625†
NISS	26.305 (180.59)	22.983 (157.3)	0.015298
GCS score	11.478 (20.747)	12.635 (15.216)	0.0090166
BAL in mg/dl	66.243 (12080)	47.424 (8161.7)	0.058688
INR‡	1.4149 (1.7697)	1.4632 (4.8853)	0.3039
Absolute platelet count in $\times 10^9/L$ §	225.4 (5776.8)	245.2 (6580.5)	0.0260
Platelet transfusion	0.092643 (0.0843)	0.056 (0.05329)	0.15369
Time to 1st HCT in hrs	4.0183 (13.04)	3.7932 (4.9244)	0.63928
Time btwn HCTs in hrs	9.2332 (69.463)	10.681 (98.05)	0.14403
Additional intracranial bleed			
EDH	0.25613 (0.19105)	0.224 (0.17523)	0.46443
SDH	0.46049 (0.24912)	0.36 (0.23226)	0.047253
SAH	0.50409 (0.25067)	0.416 (0.2449)	0.08802
Craniectomy	0.070845 (0.066)	0.088 (0.080903)	0.55151
Use of ventriculostomy	0.076294 (0.0707)	0.048 (0.046065)	0.23335
Disposition			
Home	0.4071 (0.24203)	0.54032 (0.25039)	0.010772
SNF	0.47268 (0.24994)	0.43548 (0.24784)	0.47339
Hospice/death	0.12022 (0.10606)	0.024194 (0.0238)	1.5184 $\times 10^{-5}$ †

* Values are presented as the mean (variance).

† Significant following Benjamini-Hochberg procedure ($q = 0.05$, $m = 19$).

‡ Available for 252 patients.

§ Available for 485 patients with an overall mean of 230.5, median of 226, and standard deviation of $77.74 \times 10^9/L$.

and patient disposition, first through univariate and then through multivariate analyses.

Age and Sex

Previous multivariate analyses have demonstrated a positive association between age and likelihood of HPC.^{2,6,32,42} Our univariate analysis showed a positive relationship between age and tIPH size on follow-up CT (Table 2) and expansion rate (Table 3). Our multivariate analysis also showed a positive relationship between age and odds of a death/hospice disposition (Table 4) as well as age and size of tIPH on follow-up CT (Table 5). Cepeda and colleagues hypothesized that age-associated structural weaknesses in microvasculature might lead to a higher likelihood of HPC.⁶ This explanation is consistent with our findings regarding tIPH expansion rate, patient disposition, and size of tIPH on follow-up CT.

Prior studies have found a correlation between male sex and likelihood of HPC.³² Oertel and colleagues hypothesized that this is due to neuroprotective effects of estrogen and progesterone. However, our univariate analysis showed no significant relationship between male sex and tIPH size on follow-up HCT (Table 2) or expansion rate (Table 3). Therefore, our multivariate analysis removed sex from consideration, as it had little independent predictive value for disposition (Table 4) or size of tIPH on follow-up HCT (Table 5).

Systolic Blood Pressure

In the present study, there was no significant difference in SBP between contusions that expanded and those that did not expand (Table 2), nor was there a significant difference in contusion expansion rate for SBP < 120 mm Hg compared with SBP $\geq$ 120 mm Hg (Table 3). Neither hypotension nor hypertension was found to be a significant predictor of HPC. However, on multivariate analysis, SBP was found to be negatively correlated with patient disposition to hospice or death, highlighting hypotension, identified as a 5-point decrease in SBP, as a contributor to poor patient outcome following tIPH (Table 4).

Of the studies that examined blood pressure in relation to HPC, Chang et al., Yuan et al., and Oertel et al. did not find a significant correlation between blood pressure and progressive hemorrhage or outcomes after injury.^{7,32,42} However, in a 2015 study by Kim et al., patients with HPC had a mean SBP of 134.5 mm Hg, which was significantly higher than the mean SBP in patients without HPC (119.6 mm Hg).²¹ As discussed by Oertel et al., it is possible that the management of hypotension with fluid resuscitation could in itself lead to increased bleeding or hemorrhagic progression.³² Given the findings of this study as well as the conflicting findings from prior studies, blood pressure may not independently predict HPC or the expansion rate, but it seems to play a role in more severe outcomes as determined by disposition.

TABLE 3. Univariate analysis of individual prehospital and in-hospital variables and the relationship with the ER of tIPH

Independent Variable	No. of Patients (%)	ER (ml/hr)	p Value
Age in yrs			0.0452*
<60	313 (63.7)	0.3479	
≥60	178 (36.3)	0.6999	
Sex			0.4480*
Male	351	0.5187	
Female	140	0.3671	
SBP in mm Hg			0.8726*
<120	120	0.7641	
≥120	357	0.3882	
SBP in mm Hg			0.8301†
<90	12	0.3877	
91–140	257	0.5646	
>140	208	0.3872	
Mechanism of injury			0.6268*
Fall	322	0.5311	
MVC	147	0.4546	
Assault & other	22		
GCS score			7.5189 × 10 ⁻⁵ †‡
13–15 (mild)	302	0.3484	
9–12 (moderate)	45	0.2385	
3–8 (severe)	110	0.9331	
BAL in mg/dl			0.0149*‡
0 (negative)	338	0.4142	
>0 (positive)	153	0.6109	
BAL in mg/dl			0.042†
1–150	53	0.4232	
150–250	54	0.7914	
>250	46	0.6153	
INR			0.00738*‡
≤1.2	189	0.2505	
>1.2	63	1.2352	
Absolute platelet count			0.0079*‡
<150	57	0.9365	
≥150	428	0.42	
Platelet transfusion			0.0016*‡
Yes	41	0.9417	
No	450	0.4330	
Anticoag/platelet use			0.004†‡
None	461	0.3377	
Aggrenox & Plavix	1 & 6	3.5049	
Coumadin & Dabigatran	25 & 1	1.28	
Time to 1st HCT in mins§			0.8092*
≤180	85	0.6610	
>180	88	0.3131	
Size at admission in ml			3.0605 × 10 ⁻⁷ †‡
<1	204	0.1158	
1–5	175	0.4811	
>5	112	1.1218	
Time btwn HCT in hrs			0.0099*‡
<6.5	245	0.6079	
≥6.5	246	0.3436	

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TABLE 3. Univariate analysis of individual prehospital and in-hospital variables and the relationship with the ER of tIPH

Independent Variable	No. of Patients (%)	ER (ml/hr)	p Value
Craniectomy			0.0803*
Yes	37	1.0850	
No	454	0.4258	
Ventriculostomy			0.0066*‡
Yes	34	0.9157	
No	457	0.4427	
Disposition			6.6847 × 10 ⁻¹² †‡
Home	272	0.1469	
SNF	173	0.4958	
Hospice/death	46	2.3417	

Anticoag = anticoagulant; ER = expansion rate; MVC = motor vehicle collision.

* p value of the Wilcoxon rank-sum test, which tests the null hypothesis that data in x and y are samples from continuous distributions with equal medians, against the alternative that they are not. The test assumes that the 2 samples are independent. x and y can have different lengths. This test is equivalent to a Mann-Whitney U-test.

† p value of the Kruskal-Wallis test, which tests the null hypothesis that the data in each column of the matrix x come from the same distribution. The alternative hypothesis is that not all samples come from the same distribution.

‡ Significant following Benjamini-Hochberg procedure (q = 0.05, m = 17).

§ Applicable to 173 patients.

Initial Size of Hemorrhage

Of all presenting clinical variables, the initial hemorrhage volume is perhaps the most clinically informative and prognostically relevant parameter.^{1,20} Many researchers examining HPC have identified initial tIPH volume as proportionally correlated to the amount of hemorrhagic progression, with smaller lesions remaining relatively stable while larger ones are both more likely to progress and grow by larger amounts.^{1,7,20} However, other multivariate analyses found initial hemorrhage volume to be only associated with prognosis and not volumetric progression, while one group's analysis contrarily concluded that HPC was associated with lower initial volume.^{6,20}

For our patient population, the initial volume of a pa-

TABLE 4. Ordinal response logistic regression examining patient factors that contribute to the odds that death/hospice will occur given tIPH

Variable	Coefficient	OR (95% CI)	p Value
Age (+1 yr)	0.071	1.073 (1.059–1.088)	1 × 10 ⁻²³ *
SBP (+5 mm Hg)	-0.037	0.964 (0.921–1.009)	0.113
ISS (+1 point)	0.087	1.091 (1.059–1.125)	2 × 10 ⁻⁸ *
GCS score (1 point)	-0.138	0.871 (0.820–0.926)	1 × 10 ⁻⁵ *
Follow-up scan vol (+1 ml)	0.030	1.031 (1.013–1.049)	7 × 10 ⁻⁴ *
Platelet transfusion	0.589	1.802 (0.840–3.866)	0.130
Ventriculostomy	2.693	14.782 (5.452–40.080)	1 × 10 ⁻⁷ *

* Significant following Benjamini-Hochberg procedure (q = 0.05, m = 7).

FIG. 4. Odds ratios for death/hospice for real-valued variables, including age, SBP, ISS, GCS score, and second scan volume. Whiskers indicate 95% CI. pt = point.

tient's tIPH was found to be predictive of both the rate at which a hemorrhage evolves (Table 3) and the volume of the hemorrhage on repeat HCT (Table 5).^{5,7} Table 3 demonstrates a direct correlation between the initial size of the tIPH and the expansion rate, where larger hemorrhages experience a higher rate of expansion. Furthermore, multivariate analysis identifies initial hemorrhage volume as the greatest predictor of overall expansion, accounting for nearly 31% of the predictability of hemorrhage size on repeat imaging. Overall, because the initial hemorrhage

volume is significantly associated with predicting hemorrhage volume on repeat scan and this repeat scan volume is associated with disposition, initial hemorrhage volume can be used as a surrogate not only for the extent of HPC but also for patient outcome.²⁰

Injury Scoring

Current literature presents a muddled picture of the association between GCS scores and HPC and patient outcome. Alahmadi et al. demonstrated that GCS scores at presentation independently predicted the probability of being discharged home.¹ Additionally, White et al. found that patients with normal or near-normal GCS scores were significantly less likely to experience contusion expansion and that patients with deterioration in their GCS score experienced a 3-fold increase in risk for hemorrhage expansion.⁴¹ The STICH II (trauma; second Surgical Trial in Lobar Intracerebral Hemorrhage) surgical trial demonstrated that tIPH patients with a good prognosis based on GCS scores of 13–15 can be safely observed and only require craniotomy if their condition deteriorates.²⁹ Contrary to these findings, multiple studies found no association between GCS score on admission, subsequent GCS score, or hemorrhage expansion.^{6,7,13,32,38} Juratli et al. noted that about half of their patients who experienced contusion expansion had a GCS score greater than 8 and deteriorated in the next few hours, concluding that use of GCS score alone as a decision-making tool for treatment choice may fail to provide sufficient care.²⁰ For our patient population, there was no significant difference in admission GCS score between patients who underwent repeat HCT and those who did not, which suggests that this neurological

TABLE 5. Multiple linear regression to predict volumetric expansion on follow-up HCT

Variable	Coefficient*	Multiplicative Effect (95% CI)	p Value†	Partial r ²
Age (+1 yr)	0.012	1.000 (1.000–1.000)	4×10^{-6}	0.051
NISS (+1 point)	0.022	1.023 (1.013–1.032)	4×10^{-6}	0.051
BAL (mg/dl)	0.001	1.001 (1.000–1.003)	0.005	0.019
Initial scan vol (+1 ml)	0.079	1.082 (1.070–1.095)	5×10^{-34}	0.305
Presence of EDH	0.317	1.373 (1.004–1.880)	0.048	0.010
Presence of SAH	0.424	1.529 (1.163–2.009)	0.002	0.022
Platelet transfusion	0.629	1.876 (1.281–2.749)	0.001	0.025
Ventriculostomy	0.702	2.017 (1.257–3.237)	0.004	0.020

* Overall regression of correlation coefficient of 0.529.

† Significant following Benjamini-Hochberg procedure ($q = 0.05$, $m = 8$).

FIG. 5. Quantile-quantile plot of model residuals with normal distribution represented by the line. Figure is available in color online only.

assessment did not solely inform the decision to obtain further imaging (Table 1). However, those patients who experienced HPC had a significantly lower admission GCS score, in addition to other injury severity scores (Table 2). Moreover, those patients with poor GCS scores (3–8) had significantly higher expansion rates (Table 3). Interestingly, on multivariate analysis, each point decrease in GCS score increases a patient's chance of hospice placement or death (Table 4), but GCS score was excluded in our model for predicting HPC in the acute period (Table 5). While our research found GCS scores to be a predictive factor for eventual patient outcome, it is clear that more research must be done to establish consensus on the relationship between GCS score and HPC in patients with tIPH.

Other injury scoring systems, such as the ISS, provide a global picture of the extent of a patient's injuries following trauma. In our model, a high ISS was significantly associated with HPC; thus, the greater extent of the injury the more likely a tIPH is to evolve (Table 2). Furthermore, the extent of the injury measured by such scoring systems is capable of predicting the odds of patient placement in hospice or death (Table 4) as well as the extent to which the contusion will expand in the acute setting (Table 5). Sanus et al. demonstrated that ISS was a predictive factor for eventual contusion expansion, which supports our findings, but there is a paucity of literature that examines the predictive effects of ISS on tIPH.³⁸ Nevertheless, despite the complex nature of TBI, which involves several inflammatory processes and cascades leading to neuroinflammation, the evaluation of TBI in the context of systemic trauma, including significant blood loss, adjacent soft-tissue injury, and compounded activation of proinflammatory

processes, can inform the clinician regarding the potential for HPC and overall prognosis.^{12,14,16,19,33}

Absolute Platelet Count, Platelet Transfusion, and INR

Multiple studies have found that a low platelet count at presentation, as well as prior use of antiplatelet or anticoagulation therapy, can predict HPC.^{20,27,42} However, the effects of managing low platelets with transfusion have not been examined with relation to HPC or expansion rate. Patients in our study had an average absolute platelet count of $230.5 \times 10^9/L$, while only 8.3% received a platelet transfusion. There was a significantly lower ($p = 2.672 \times 10^{-7}$) absolute platelet count in those patients who received a platelet transfusion ($163.6 \times 10^9/L$) compared with those who did not undergo transfusion ($236.5 \times 10^9/L$). Although there is no protocol for platelet transfusion with TBI at our institution, leaving this administration to physician discretion, a low absolute platelet count is significantly related to a transfusion of platelets. Patients in our study who were on a regimen antiplatelet or anticoagulation therapy prior to presentation had a higher expansion rate (Table 2), as expected based on prior studies. Our analysis also shows that neither platelet administration nor initial INR were independently correlated with HPC, yet a lower absolute platelet count was correlated with HPC (Table 2). However, among patients with HPC, those who had an absolute platelet count lower than $150 \times 10^9/L$, those who received platelet transfusions, and those who had a higher initial INR exhibited a faster rate of expansion (Table 3). Platelet administration is predictive of second scan size (Table 5) but is not predictive of clinical

outcome or disposition (Table 4), a finding that is in line with prior studies.^{8,17,40}

As posited by Washington et al., platelet transfusion during tIPH confers no clinical benefit due to the side effects of the intervention itself, such as trauma-related lung injury. Additionally, it is hypothesized that platelet transfusion, although intended to reverse pre-tIPH antiplatelet therapy, does not actually inhibit the effects of the antiplatelet activity and would require multiple transfusions to overwhelm those effects to provide any reversal.⁴⁰ Therefore, given the current literature and our findings, platelet transfusion in the setting of tIPH may not provide any clinical or radiological benefit, while a lower absolute platelet count is associated with HPC and increased expansion rate.

Blood Alcohol Level

Ethanol has been widely recognized for its antiplatelet effects. Older studies point to the potentiating effects of ethanol on prostacyclins, which have inherent antiplatelet properties.^{11,18,28,30} Newer molecular studies have identified impaired calcium entry into platelets as the mechanism by which ethanol prevents platelet aggregation, rendering them dysfunctional.^{9,26,34} For these reasons, the effects of ethanol on platelet function must be considered when patients present with clinically significant hemorrhage. Here, differences in the mean BAL did not reach significance in patients with HPC compared with those with no HPC (Table 2), although there was a nonsignificant correlation between higher BAL and hemorrhagic progression. Similarly, neither Oertel et al. nor Juratli et al. identified BAL as a predictor of HPC.^{20,32} BAL has not yet been studied as a predictor of expansion rate or radiological outcomes. Our results demonstrate that a higher BAL is univariately correlated with an elevated expansion rate (Table 3) and, on multivariate analysis, is predictive of size on the second scan (Table 5). These findings are unsurprising, given the biochemical and molecular studies that describe the antiplatelet properties of ethanol.

Additional Intracranial Trauma

Multiple other studies have demonstrated a correlation between HPC and additional intracranial hemorrhages, such as SAH, SDH, and EDH. Alahmadi et al. demonstrated that the presence of coexisting SDH was a significant predictor for contusion progression, while Juratli et al. reported that worsening prognosis was found among patients with acute SDH.^{1,20} In addition, Chang et al. demonstrated that HPC was independently associated with the presence of SAH and SDH. Furthermore, they presented a statistically significant association between tIPH growth and the presence of additional hemorrhage subtypes.⁷ On univariate analysis, there was a statistically significant relationship between HPC and the presence of SDH. Multivariate analysis did not establish that presence of any additional type of hemorrhage was predictive of patient outcome; however, the presence of EDH and SAH were both independently predictive of tIPH volume on the second scan. While the literature presents a fairly clear consensus that the presence of additional hemorrhage subtypes is correlated with HPC and worsened patient outcomes, there is

no clear single category of hemorrhage that appears significantly more predictive than others.

Craniotomy and Craniectomy

Previous multivariate analysis has demonstrated a positive association with decompressive craniotomy and the likelihood of HPC. Cepeda and colleagues hypothesized that this is due to the tamponade effect of removing a bone flap.⁶ In contrast, our univariate analysis showed no significant relationship between craniotomy or craniectomy and tIPH volume on follow-up HCT (Table 2) or expansion rate (Table 3). Our multivariate analysis removed decompressive craniotomy or craniectomy from consideration, as it had little independent predictive value for disposition (Table 4) or size of tIPH on follow-up CT (Table 5). This is likely due to the small number of patients ($n = 37$) who underwent this procedure in our study population.

Ventriculostomy

There is a dearth of multivariate analysis on the effects of ventriculostomy on HPC or dispositions in the literature. Our univariate analysis did not show a significant association between ventriculostomy and tIPH volume on follow-up CT (Table 2) but showed a significant positive relationship between ventriculostomy and tIPH expansion rate (Table 3). Our multivariate analysis showed a positive association between use of ventriculostomy and odds of a death or hospice disposition (Table 4) as well as use of ventriculostomy and size of tIPH on follow-up CT (Table 5). We believe this is likely due to endogenous factors not captured by our data set. Patients underwent ventriculostomy likely on the basis of other clinical criteria associated with worse outcomes.

Strengths and Limitations

Our study has several limitations regarding its ability to identify variables that affect HPC, predict patient outcome, and predict the volumetric expansion after tIPH. First, this is a retrospective study with a narrow follow-up period limited to the disposition of the current hospitalization. Without long-term follow-up data, we are unable to assess the functional outcome, in addition to the morbidity and mortality, of TBI after the acute period. Furthermore, due to incomplete data collection on admission, 69 of the 491 patients had to be excluded from all multivariate analyses due to missing prehospital and/or in-hospital characteristics. Second, there is a selection bias of those patients with 2 scans, both admission and follow-up HCT sessions. Third, various unknown confounding factors from a patient's medical history, such as the use of illicit substances, previous TBI, or a history of congenital clotting disorders, could potentially lead to HPC and were not included in our analysis. Finally, there is no formal protocol for the transfusion of platelets with TBI at our institution, leaving their administration to physician discretion. Despite these limitations, our study volumetrically examines a large and diverse patient population from a level 1 trauma center. Like other studies examining HPC, we identified various factors that contribute to this expansion; however, we also investigated how these clinical factors relate to the rate of

contusion expansion and the disposition of patients following TBI.

Furthermore, rather than a rudimentary cross-sectional measurement, our 3D volumetric measurements of hemorrhages sought to evaluate HPC in a more quantitative manner than previously attempted. Cutoffs for HPC used in prior works include +0%,⁷ +25%,^{32,42} +30%,⁶ and +33%.^{2,41} Oertel et al. and Yuan et al. looked for progression along any one dimension.^{32,42} Chang, Cepeda, White, and Allison and their coauthors calculated intraparenchymal volumes using $(A \times B \times C)/2$.^{2,6,7,41} Conservative cutoffs (i.e., > +0%) are often employed to account for differences in patient placement that could affect the lengths used in the volume calculation. In contrast, our methodology sums the exact cross-sectional volumes, and thus our numbers would not be affected by the particular image slice selection or presence of nonellipsoid hemorrhages.

Conclusions

TBI, including tIPH, remains a significant worldwide cause of morbidity and mortality. Unique to tIPH, these traumatic lesions can progress over time and cause a mass effect on various structures, thereby resulting in severe and debilitating injury. The results presented provide further evidence that particular variables (age, injury severity, GCS score, BAL, concomitant SDH) are present in the expanding-hemorrhage population, while similar patient characteristics (i.e., age, GCS score, BAL, INR, platelet transfusion, anticoagulant/antiplatelet medication, initial hemorrhage volume, and ventriculostomy) individually contribute to the rate at which traumatic cerebral contusions blossom over an acute time course. Furthermore, we employed retrospective data to predict patient outcome and the acute volumetric expansion after tIPH, given a patient's prehospital and in-hospital characteristics. Understanding the relationship of these characteristics of the presenting patient can help predict the rate of expansion and highlight potential therapeutic interventions to improve TBI-associated morbidity and mortality.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Carnevale, Segar, Powers, Shah, Morrison, Asaad. Acquisition of data: Carnevale, Segar, Powers, Doberstein, Drapcho, Williams, Collins. Analysis and interpretation of data: Carnevale, Segar, Powers, Shah, Doberstein, Drapcho, Williams, Asaad. Drafting the article: Carnevale, Powers, Shah, Doberstein, Drapcho. Critically revising the article: Carnevale, Segar, Powers, Doberstein, Morrison, Collins, Monteiro, Asaad. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Carnevale. Statistical analysis: Carnevale, Segar, Powers, Shah, Monteiro, Asaad. Administrative/technical/material support: Carnevale. Study supervision: Carnevale, Asaad.

Supplemental Information

Previous Presentations

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